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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/306,662	05/05/99	MALMROS	M PRO-SE

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EXAMINER	
RAWLINGS,S	
ART UNIT	**PAPER NUMBER**
1642	8

DATE MAILED: 01/30/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/306,662	MALMROS ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-19 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-19 is/are rejected.

7)☒ Claim(s) 7, 10, 13, and 19 is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2 .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

DETAILED ACTION

1. The Election without traverse in response to the Office Action mailed September 29, 2000 (Paper No. 3) is acknowledged and has been entered. Applicant elects the claims drawn to the species comprising skin. Claims 1-19 are pending in the application and are currently under prosecution.

Specification and Claim Objections

2. The specification and claims 7 and 13 are objected to because of the following informalities:

The terms "metaplasic" and "dysplasic" appear to be misspellings of the terms "metaplastic" and "dysplastic". Appropriate correction is required.

3. Claims 10 and 19 are objected to because of the following informalities:

The use of the term "vaginal" is incorrect because the context of the sentence requires the use of a term denoting an internal organ (i.e. the term "vagina" should be substituted in the claim for the term "vaginal").

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in

such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method for making an *in situ* diagnosis or analysis of biological tissue and cells of living organisms.

The specification teaches that "the use of biological stains in direct staining *in vivo* has been shown to have a high degree of sensitivity to a variety of metaplasic, pre-cancerous, and cancerous cells and tissues" (page 20, lines 3-5). The specification teaches general methods of applying reflectance spectroscopy to diagnose and/or treat diseased tissue and/or cells (pages 20-23), comprising the direct application of a stain to living tissue, wherein the properties and characteristics of the stain is controlled (page 20, lines 19-22) and further comprising irradiation of the stained tissue, collection and measurement of reflected light (page 20, line 29 to page 21, line 4), and analysis of the data by software means using a microcomputer (page 21, lines 4-8).

One cannot extrapolate the teachings of the specification to the enablement of the claims because one of skill in the art can not determine how the invention is to be specifically practiced. The specification teaches that "the specificity of the staining process in differentiating between the stage and type of metaplasia has been variable and has **not** [emphasis added] allowed for a definitive diagnosis of the disease state" (page 20, lines 8-10). Further, the specification teaches that "vital or *in vivo* staining has **not** [emphasis added] been able to distinguish between normal cellular repair processes and metaplasia" (page 20, lines 10-11). However, the specification does not provide sufficient guidance with regard to these

issues; nor does it propose or explain the rationale by which these shortcomings or misconceptions are rendered solved by the claimed invention or to be considered inaccurate. Moreover, the specification does not teach that the method can be applied to any particular tissue type or cell type, and to which, if any, of these tissues and cells the method can not be applied. The specification provides no working examples that would provide guidance to one skilled in the art to use the invention. Accordingly, no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed method or to use the invention, commensurate in scope with the claims, with a reasonable expectation of success.

In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

6. Claims 13-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of cytotoxic destruction of dysplastic, pre-cancerous, or cancerous cells *of the skin*, does not reasonably provide enablement for a method of cytotoxic destruction of dysplastic, pre-cancerous, or cancerous cells *in any tissue*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to a method for the cytotoxic destruction of dysplasic, pre-cancerous or cancerous cells and tissues comprising photodynamic therapy.

The specification teaches as set forth above and cites a reference that teaches that photodynamic therapy has been applied to the treatment of skin lesions (see page 13, lines 1-3).

One cannot extrapolate the teachings of the specification to the scope of the claims because one of skill in the art can not determine how the invention is to be specifically practiced. Moreover, one of skill in the art would not have a reasonable expectation of success in practicing the invention, absence any teaching to the contrary in the specification, because it is widely known in the art that the cytotoxic destruction of select tissues by photodynamic therapy is ineffective. For example, Nseyo, et al (*Urology* **36**: 398-402, 1990) teach:

> Present-day whole bladder photodynamic therapy (WBPDT) is cumbersome and time consuming because cystoscopic and ultrasonic manipulations are necessary to position the light emitter within the bladder. More important, WBPDT is inherently unsafe and often ineffective since neither uniform photoirradiation nor accurate light dosimetry can be achieved with the techniques employed to photoirradiate the bladder wall.

Although drawn specifically to treatment of bladder disease, the teachings of the reference cited above can be applied to any intracorporeal tissue or organ.

Also, since the claimed method of photodynamic therapy requires contacting targeted cells with a stain or dye, there are additional problems which limit the efficacy of the method that need be addressed. For example, the refractory nature of cancer to drugs is well known in the art.

Jain (*Scientific American* **271**: 58-65, 1994) teaches that most tumors resist full penetration by anticancer agents (page 58, column 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (page 65, column 3). Curti (Critical Reviews in Oncology/Hematology 14: 29-39, 1993) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited. Curti also teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and, if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (paragraph bridging pages 29-30). Curti concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (page 36, column 2). Thus, it is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the method would function effectively to selectively eradicate dysplastic, pre-cancerous, or cancerous cells from intracorporeal tissues and organs.

In addition, Hartwell, et al (*Science* **278**: 64-1068, 1997) teach that an effective chemotherapeutic must selectively kill tumor cells, that most anticancer drugs have been discovered by serendipity, and that the molecular alterations that provide selective tumor cell killing are unknown. Hartwell, et al teach that even understanding the detailed molecular

mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (paragraph bridging pages 1064-1065) and Jain (cited supra) specifically teaches that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (page 58, column 2). It appears that the compositions of the method are not selective for tumor cells nor would it be expected that the formulation would act only on dividing cells, since the dye or stain would be taken up by normal cells and tissues.

Furthermore, anti-tumor agents must accomplish several tasks to be effective. They must be delivered into the circulation that supplies the tumor and interact at the proper site, and they must do so at a sufficient concentration and for a sufficient period of time so as to be effective. Also, the targeted cells must not have an alternate means of survival despite action at the proper site for the drug. In addition, variables such as biological stability, half-life, and clearance from the blood are important parameters in achieving successful therapy. The composition may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation, or due to an inherently short half-life. The composition may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted. Alternatively, the composition may be absorbed by fluids, cells and tissues where the formulation has no effect and circulation into the target area may be insufficient to carry the composition and to permit a large enough local concentration to be established.

Finally, Gura (*Science* **278**: 1041-1042, 1997) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile (abstract). Gura teaches that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models, but that only 39 have actually been shown to be useful for chemotherapy (page 1041, first and second paragraphs). However, it is noted that the specification does not teach which, if any metachromatic dye or stain is efficacious in treating a cell or an animal model, let alone, a human.

The specification does not provide sufficient guidance with regard to these issues; nor does it propose or explain the rationale by which these shortcomings or misconceptions are rendered solved by the claimed invention or to be considered inaccurate. Furthermore, the specification does not teach that how the method can be applied to any particular tissue type or cell type, and to which, if any, of these tissues and cells the method cannot be applied.

Moreover, the specification provides no working examples that would provide guidance to one skilled in the art to use the invention. Accordingly, no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed method or to use the invention, commensurate in scope with the claims, with a reasonable expectation of success.

In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-11 are indefinite because claim 1 recites the phrase, "a method for making an *in situ* analytical diagnosis of biological tissue and cells". Claim 1 and claims that depend upon claim 1 are rendered indefinite by this phrase since one does not ordinarily make a diagnosis of biological tissue and cells; rather, one generally makes a diagnosis of a disease or a disease state or a cellular condition. Thus, it cannot be determined what disease or cellular state is being analytically diagnosed by the claimed method and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

9. Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "suitable" in claim 1 is a relative term that renders the claim indefinite. The term "suitable" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Amending claim 1 to delete the term "suitable" can obviate the rejection.

10. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because the claim recites the phrase, "with previously obtained spectrum" in line 10. Claim 1 is rendered indefinite by this phrase since it cannot be determined from which tissue or cells that said previously obtained spectrum will be obtained prior to steps (a) and (b) and from what source said tissue and cells are derived. The specification does not provide sufficient guidance in this matter and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

11. Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 is indefinite because the claim recites the phrase, "classified by means of conventional histochemical and biochemical techniques". Claim 6 is rendered indefinite by this phrase since it cannot be determined what aspects or characteristics of the tissues or cells are being classified or how the tissues or cells are being classified by the claimed method. The classification scheme is not defined by the claim, the specification does not provide a standard for ascertaining the nature classification scheme, and

one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

12. Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "otherwise abnormal" in claim 7 is a relative term that renders the claim indefinite. The term "otherwise abnormal" is not defined by the claim nor does the specification provide a standard for ascertaining the requisite degree of abnormality and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Regarding claim 7, the phrase "or otherwise abnormal" is indefinite because it reads on the phrase "or the like", which renders the claim indefinite because the claim includes elements not actually disclosed (those encompassed by the term "or the like"), thereby rendering the scope of the claim unascertainable. See MPEP § 2173.05(d).

13. Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 is indefinite because the claim recites the phrase, "a method for making an *in situ* analysis of biological tissue and cells" in lines 1-2. Claim 12 is rendered indefinite by this phrase since it cannot be determined what aspect or characteristic of the tissue and cells is being analyzed by the claimed method. The aspect or characteristic of the tissue and cells is

not defined by the claim, the specification does not provide a standard for ascertaining the nature of said disease or cellular state, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 12 is also indefinite because it recites the phrase "the changes of the reflected light spectrum" in line 6. The aspect or characteristic of the spectrum that is undergoing a change (e.g. wavelength, intensity, amplitude, frequency, etc.) has not been defined and cannot be determined from the specification and furthermore, it cannot be determined relative to what reference the change occurs.

Claim 12 is further rendered indefinite by the recitation of the phrase "correlating" in line 7. The measurement or determination that is to be correlated with said change has not been defined and cannot be determined. This particular rejection can be obviated by substituting the phrase "identifying" for the phrase "correlating" in line 7 of claim 12.

14. Claims 13-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 13-19 are indefinite because claim 13 recites the terms "suitable" and "sufficient". The terms "suitable" and "sufficient" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 13 and claims that depend upon claim 13 are rendered indefinite by this phrase since it cannot be determined what constitutes a suitable and sufficient intensity and quality.

Claim 13 is also indefinite because it recites the phrase "the change of the reflected spectrum" in line 6. The aspect or characteristic of the spectrum that is undergoing a change has not been defined and cannot be determined. Therefore, claim 13 and the claims that depend upon claim 13 are indefinite.

15. Claim 17 recites the limitation "the spectrometer" in line 1. There is insufficient antecedent basis for this limitation in the claim or in the claim upon which it depends.

16. Claims 1-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-19 are indefinite because in claims 1 and 12-13 there is no positive process step that clearly relates back to the preamble of the respective claims.

Amending claims in the last line to recite a positive process step can obviate the rejection; for example, the last line of claim 1 could be amended to read, "whereby an *in situ* diagnosis of a disease state is made".

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. Claims 1-19 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by US 5,784,162 A, as evidenced by Vaezy, et *al (Journal of Microscopy* **163**: 85-94, 1991) and Marchesini, et *al (Photochemistry and Photobiology* **55**: 515-522, 1992).

Claims 1-11 are drawn to a method for making an *in situ* analytical diagnosis of biological tissue and cells of living organisms comprising applying to the tissue or cells a stain or dye, measuring and recording light reflected from the surface of said tissue or cells using a spectrometer, and comparing the reflected spectrum with a reflected spectrum previously determined (claim 1), wherein the stain or dye is one or a combination of more than one stain or dye (claim 2), or wherein said stain or dye is metachromatic (claim 3), or wherein the stain or dye is a combination of stains or dyes, one of which is metachromatic (claim 4), or wherein said spectrum is compared to a database file of spectrums by a software means (claim 5) wherein the database consists of files containing the spectrums of tissue or cells similarly stained, analyzed, and classified by conventional means (claims 6) and wherein the spectrum of normal unstained tissue or cells is first subtracted form the spectrum of the stained tissue or cells

(claim 11), or wherein the tissues or cells are thought to be diseases, metaplastic, or otherwise abnormal (claim 7), or wherein the spectrometer is able to measure light of a specifically claimed range of wavelengths (claim 8), or wherein the spectrum is measured and recorded by means of a photometer and a filter(s) (claim 9), or wherein the tissues or cells are of the skin (claim 10). Claim 12 is drawn to a method for making an *in situ* analysis of biological tissue and cells of living organisms and correlating the change in the reflected spectrum. Claims 13-19 are drawn to a method for the cytotoxic destruction of dysplastic, pre-cancerous, or cancerous cells and tissues, comprising applying to said cells or tissues a stain or dye, irradiating said cells or tissues, and simultaneously monitoring the change of the reflected spectrum (claim 13), wherein the stain or dye is one or a combination of more than one stain or dye (claim 14), or wherein the stain or dye is metachromatic (claim 15), or wherein the stain or dye is a combination of stains or dyes, one of which is metachromatic (claim 16), or wherein the spectrometer is able to measure light of a specifically claimed range of wavelengths (claim 17), or wherein the spectrum is measured and recorded by means of a photometer and filter(s) (claim 18), or wherein the tissue or cells are of the skin (claim 19).

US 6,096,873 A specifically discloses a spectral bio-imaging system that consists of a measurement system and analysis software (column 2, lines 3-12). The reference teaches spectral imaging methods for *in situ* medical diagnosis and treatment comprising preparing a sample to be imaged, viewing the sample through an optical device optically connected to a spectrometer, collecting and measuring incident light using a detector,

and collecting and interpreting data using a mathematical algorithm (abstract and claim 54 of the prior art).

Importantly, the reference specifically teaches that the collimated incident light may be light *reflected* by the sample (column 39, lines 56-58; see claim 5 of the prior art also).

The reference teaches that the spectral bio-imaging systems can be used to compare the spectrum of reflected light and, therefore, are useful in all applications in which subtle spectral differences exist between chemical constituents whose spatial distribution and organization within an image are of interest (column 5, lines 22-26). Furthermore, numerous examples of *in situ* analyses of cells and/or tissues to either classify and/or diagnose cellular abnormalities in said cells and/or tissues are provided in the reference (in particular, see Examples 1, 6, 7, and 8). It is noted that Example 1 teaches an *in situ* analysis of a living cellular organism, but many examples of analysis of living cells and tissues are offered (see claims 11 and 17 of the prior art also). The reference teaches the advantage of the prior art invention is that it allows comparisons to be made (see column 60, line 57 to column 61, line 1).

The reference also teaches numerous methods of mathematical correlation (columns 19-25) and in particular, discloses that the mathematical algorithm can be a similarity mapping analysis program for computing a spectral difference from a reference spectrum (column 9, lines 12-16) or from several reference spectra (column 9, lines 33-37). The reference teaches that collected data could be correlated since the mathematical algorithm can compute a ratio between intensities at two

different wavelengths (column 10, lines 39-42) or the algorithm can be a linear combination analysis (column 9, line 65 to column 10, line 27).

As a specific example of a correlative analysis of data, the reference teaches (see Example 2, columns 43, line 63 to column 44, line 4):

> The purpose of this example is to show the SpectraCube™ system combined with the methods of the present invention abilities to acquire multiplex spectroscopic information from nuclei of human erythropoietic bone marrow cells and to correlate the spectroscopic data with chromatin condensation.

Anticipating the limitations in claims 2-4, the reference teaches that the prior art method can be used for spectral identification of multiple fluorophores administered to cells or a tissue (column 10, lines 49-51). The reference also discloses that a fluorescent dye, acridine orange, can be used in practicing the prior art invention; and it teaches that acridine orange dye is metachromatic, undergoing a spectral shift as a result of energy transfer between the molecules of dye and the surrounding chemical environment (column 33, line 49 to column 34, line 2). The reference teaches that, as a further example of metachromatic dyes, Azure-B, a thiazine dye, could be used to practice the prior art methods (see Example 2, column 43, line 10). The reference also teaches that the spectral imaging methods of the prior art invention can be used to monitor a combination of several fluorophores, such as acridine orange, simultaneously, in one measurement (column 1, lines 61-63).

Anticipating the limitations in claim 5, the reference teaches that a computer can be used to measure and memorize (i.e. store) bio-imaging

data points in a database file by means of software and a microprocessor (column 60, lines 29-39). Additionally, in column 61, lines 25-28, the reference teaches that "an integral part of the present invention are also a number of mathematical algorithms that the computer software employs to interpret and display the data in a meaningful way". Although, the reference does not specifically indicate that a database, per se, is used to store the imaging data points, it is generally known in the art that software programs used to store large quantities of data points are otherwise known as databases. It is further noted that it is well known in the art that a computer comprises a microprocessor.

In anticipation of the limitations of claim 6, which depends upon claim 5, the reference teaches that the sample of tissue or cells to be analyzed is prepared by staining with either Romanowsky-Giemsa stain, haematoxylin-eosin stain, or May-Grunwald-Giemsa stain (see claim 59). It is noted that each of above staining procedures is conventional. The reference also teaches that histological samples can be analyzed (column 5, lines 47-50) to create spectral signatures suitable for identification and classification (column 22, line 18 to column 24, line 35). The reference specifically teaches in column 38, lines 47-54 that a spectral component may "correlate well with what is called 'the purple Romanowsky-Giemsa complex' ". As set forth above, the reference anticipates the use of databases to organize and store data points acquired in analyses of tissues and cells for subsequent classification purposes.

Anticipating the limitations of claim 7, the reference teaches that an objective of the prior art invention is to distinguish cancer from healthy or otherwise diseased tissue or cells (column 6, lines 27-33).

In regard to the limitations in claim 8, it is noted that it is well known in the art that spectrometers are able to measure light at a given wavelength within the claimed range of wavelengths (i.e. 200-1100 nanometers). It is further noted that this particular range of wavelengths is the so-called "scattering range" of visible light spectral energy, as evidenced by Vaezy, et al, which would be expected to comprise the reflected light spectrum. In support of the assertion that an inherent feature of the typical reflectance spectrophotometer is a capability of measuring reflected light in this range of wavelengths, see Marchesini, et al. However, it is also noted that the prior art reference specifically teaches that measurements in this range of wavelengths were made (see, for example, column 41, lines 61-63 and column 59, lines 56-63).

The limitations of claim 9 require that the measurements be made and recorded by means of a photometer and one or more light filters. It is noted that a spectrometer comprises a photometer and it is well known in the art that a spectrophotometer can comprise filters that disperse light of specific wavelengths for quantification by a photometer. However, the prior art reference specifically teaches that the imaging system can comprise filters; for example, it teaches that image lowpass filters are used in analysis (see Example 2, column 43, lines 37-40). The reference also teaches that a photometer is used to measure illumination (see Example 3, column 46, lines 65-67).

In anticipation of the limitations in claim 10 and in light of the election of species, the reference specifically teaches that the tissue can be of any type, including the skin (column 40, lines 7-10). Moreover, the reference teaches that a photosensitizing dye can be applied topically to the skin in preparation of phototherapy (see Example 3, column 46, line 13).

Anticipating the limitations in claim 11, the prior art reference teaches that the method requires background subtraction (column 61, line 42 and claim 40). In claim 27, the reference teaches that an analysis of data acquired requires determination of the spectral difference relative to a reference spectrum. The reference teaches that "a calibration procedure in which a spectrum measured prior to sample analysis is used" is also required (column 21, line 65 to column 22, line 4).

In regard to claim 12, it is noted that a method for making an *in situ* diagnosis of a disease state in a tissue or cells would necessarily entail making an *in situ* analysis of said tissue or cells; thus, to the extent that the prior art reference anticipates claim 1, the reference anticipates claim 12. However, it is noted that in step (c), claim 12 differs from claim 1 in that the change in the reflected light spectrum is correlated as a cytochemical or histochemical property of a particular tissue or cell type. While this recitation is considered to be indistinct (see the USC §112, second paragraph rejections above), for the purpose of examination, the claim is interpreted to encompass a method in which cells or tissues are classified by means of measuring the change in the reflective properties of said cells or tissues after staining said cells or tissues with a dye according to said change. To this extent of this limitation, US 5,784,162 A anticipates the

claim teaching a method of cell classification (see Example 8, column 58 and Claim 69).

The reference anticipates claims 13-19 teaching that the methods could be practiced to treat skin cancer (i.e. melanoma), whereby photodynamic therapy causes the destruction of cancer cells contacted by a stain, 5-aminolevulinic acid (5-ALA), that is a highly potent photosensitizer (column 46, line 8-9). The reference teaches that 5-ALA "has been shown as highly selective both in demarcating the tumor and in its photodestruction" (column 46, lines 14-15). In claim 54, the prior art teaches that "skin imaging can be performed before, during, and after a photodynamic therapy treatment. As set forth above, US 5,784,162 A anticipates the additional limitations recited in the claims that depend upon claim 13.

Therefore, in view of the teachings of the prior art reference, all the limitations of the claims are met.

Conclusion

19. No claims are allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Thursday, alternate Fridays, 8:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703)

308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Art Unit 1642

slr
January 18, 2001